Amendments to the Specification:

At Page 16, lines 29-30, please insert the following paragraphs:

--Among other synthesis methods, PCT Application No. 93/09668 discloses a method to synthesize an array using a spotting technique. According to one aspect of the invention, a substrate is provided which has an array of discrete reaction regions separated from one another by inert regions. In one embodiment, a first monomer solution is spotted on a first set of reaction regions of a suitably derivatized substrate. Thereafter, a second monomer solution is spotted on a second set of regions, a third monomer solution is spotted on a third set and so on, until a number of the regions each have one species of monomer located therein. These monomers are reacted with the surface, and the substrate is subsequently washed and prepared for reaction with a new set of monomers. Dimers, trimers, and larger polymers of controlled length and monomer sequence are prepared by repeating the above steps with different groupings of the reaction regions and monomer solutions.

The "spotting" embodiments of PCT Application No. 93/09668 can be implemented in much the same manner as flow channel embodiments shown in the application. For example, a monomer A can be delivered to and coupled with a first group of reaction regions which have been appropriately activated. Thereafter, a monomer B can be delivered to and reacted with a second group of activated reaction regions. Unlike the flow channel embodiments described above, reactants are delivered by directly depositing (rather than flowing) relatively small quantities of them in selected regions. In some steps, of course, the entire substrate surface can be sprayed or otherwise coated with a solution. In preferred embodiments, a dispenser moves from region to region, depositing only as much monomer as necessary at each stop. Typical dispensers include a micropipette to deliver the monomer solution to the substrate and a robotic

system to control the position of the micropipette with respect to the substrate. In other embodiments, the dispenser includes a series of tubes, a manifold, an array of pipettes, or the like so that various reagents can be delivered to the reaction regions simultaneously.

According to some embodiments, monomers (or other reactants) are deposited from a dispenser in droplets that fill predefined regions. For example, in a single coupling step, the dispenser deposits a first monomer in a series of predefined regions by moving over a first region, dispensing a droplet, moving to a second region, dispensing a droplet, and so on until the each of the selected regions has received the monomer. Next the dispenser deposits a second monomer in a second series of predefined regions in much the same manner. In some embodiments, more than one dispenser may be used so that more than one monomer are simultaneously deposited. The monomers may react immediately on contact with the reaction regions or may require a further activation step, such as the addition of catalyst. After some number of monomers have been deposited and reacted in predefined regions throughout the substrate, the unreacted monomer solution is removed from the substrate. This completes a first process step.

For purposes of this embodiment, the spacing between the individual reaction regions of the substrate preferably will be less than about 3 mm, and more preferably between about 5 and 100 μm. Further, the angular relation between the regions is preferably consistent to within 1 degree and more preferably to within 0.1 degree. Preferably, the substrate will include at least about 100 reaction regions, more preferably at least about 1000 reaction regions, and most preferably at least about 10,000 reaction regions. Of course, the density of reaction regions on the substrate will vary. In preferred embodiments, there are at least about 1000 reaction regions per cm^2 of substrate, and more preferably at least about 10,000 regions per cm^2.

To deposit reactant droplets consistently at precisely specified regions, a frame of reference common to the delivery instrument and the substrate is required. In other words, the reference coordinates of the instrument must be accurately mapped onto the reference coordinates of the substrate. Ideally, only two reference points on the substrate are necessary to map the array of polymer regions completely. The dispenser instrument locates these reference points and then adjusts its internal reference coordinates to provide the necessary mapping. After this, the dispenser can move a particular distance in a particular direction and be positioned directly over a known region. Of course, the dispenser instrument must provide precisely repeatable movements. Further, the individual regions of the array must not move with respect to the reference marks on the substrate after the reference marks have been formed. Unfortunately, pressing or other mechanical operations commonly encountered during fabrication and use of a substrate can warp the substrate such that the correspondence between the reference marks and the reaction regions is altered.

Control of the droplet size may be accomplished by various techniques. For example, in one embodiment, a conventional micropipetting instrument is adapted to dispense droplets of five nanoliters or smaller from a capillary. Such droplets fit within regions having diameters of 300 μm or less when a non-wetting mask of the invention is employed.

In another embodiment, the dispenser is a piezoelectric pump that generates charged droplets and guides them to the reaction region by an electric field in a manner analogous to conventional ink-jet printers. In fact, some ink-jet printers can be used with minor modification by simply substituting a monomer containing solution for ink. For example, Wong et al., European Patent Application 260 965, incorporated herein by reference for all purposes, describes the use of a commercial printer to apply an antibody

to a solid matrix. In the process, a solution containing the antibody is forced through a small bore nozzle that is vibrating in a manner that fragments the solution into discrete droplets. The droplets are subsequently charged by passing through an electric field and then deflected onto the matrix material.

A conventional ink drop printer includes a reservoir in which ink is held under pressure. The ink reservoir feeds a pipe which is connected to a nozzle. An electromechanical transducer is employed to vibrate the nozzle at some suitable high frequency. The actual structure of the nozzle may have a number of different constructions, including a drawn glass tube which is vibrated by an external transducer, or a metal tube vibrated by an external transducer (e.g. a piezoelectric crystal) or a magnetostrictive metal tube which is magnetostrictively vibrated. The ink accordingly is ejected from the nozzle in a stream which shortly thereafter breaks into individual drops. An electrode may be present near the nozzle to impart a charge to the droplets. Conventional ink drop dispensers are described in U.S. Pat. Nos. 3,281,860 and 4,121,222, which are incorporated by reference herein for all purposes.

In a different preferred embodiment, the reactant solutions are delivered from a reservoir to the substrate by an electrophoretic pump. In this device, a thin capillary connects a reservoir of the reactant with the nozzle of the dispenser. At both ends of the capillary, electrodes are present to provide a potential difference. As is known in the art, the speed at which a chemical species travels in a potential gradient of an electrophoretic medium is governed by a variety of physical properties, including the charge density, size, and shape of the species being transported, as well as the physical and chemical properties of the transport medium itself. Under the proper conditions of potential gradient, capillary dimensions, and transport medium rheology, a hydrodynamic flow will be set up within the capillary. Thus, in an electrophoretic pump of the present

invention, bulk fluid containing the reactant of interest is pumped from a reservoir to the substrate. By adjusting the appropriate position of the substrate with respect to the electrophoretic pump nozzle, the reactant solution is precisely delivered to predefined reaction regions.--